

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188
<p>Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.</p>			
1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED	
	23.Mar.05	MAJOR REPORT	
4. TITLE AND SUBTITLE	RING-CLOSING METATHESIS OF MACROCYCLIC COMPOUNDS AND CROSS-METATHESIS OF ALLYL ESTERS OF AMINO ACIDS LEADING TO PEPTIDOMIMETICS		5. FUNDING NUMBERS
6. AUTHOR(S)	CAPT LOW TAMMY K		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	UNIVERSITY OF FLORIDA		8. PERFORMING ORGANIZATION REPORT NUMBER  CI04-1008
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	THE DEPARTMENT OF THE AIR FORCE AFIT/CIA, BLDG 125 2950 P STREET WPAFB OH 45433		10. SPONSORING/MONITORING AGENCY REPORT NUMBER
11. SUPPLEMENTARY NOTES			
12a. DISTRIBUTION AVAILABILITY STATEMENT Unlimited distribution In Accordance With AFI 35-205/AFIT Sup 1		12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words)			
14. SUBJECT TERMS			15. NUMBER OF PAGES 3
			16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

**TOPIC:** Combinatorial, Parallel, and Solid Phase Chemistry

**TITLE:** Ring-Closing Metathesis of Macrocyclic Compounds and Cross-Metathesis of Allyl Esters of Amino Acids Leading to Peptidomimetics

**AUTHORS:** Tammy K.C. Low and Eric Enholm

The preparation of a dynamic combinatorial library of peptides using the cross-metathesis of allyl esters of amino acids was examined in a model study. This preliminary investigation employed Grubbs' second generation catalyst for the ring-closing metathesis of unique macrocyclic systems. An N-allyl lactam function, that was part of the large ring, was reacted with allyl esters of amino acids in a cross-metathesis coupling. The reversibility of the reaction, the modified amino acids, and the dynamic biomimetic aspects were all of interest in this study on new types of cyclic peptidomimetics.

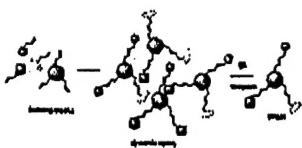
20050328 017

**Ring-Closing Metathesis of Macroyclic Compounds and Cross-Metathesis of Allyl Ester of Amino Acids Leading to Peptidomimetics**

TAMMY K.C. LOW and ERIC J. ENHOLM  
DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MONTANA, GALLUPVILLE, 59834

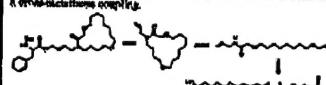
**INTRODUCTION**

Ring-closing and cross-metathesis reactions are important tools in organic synthesis. The feasibility of cross-metathesis makes it ideal for use in dynamic combinatorial chemistry. In particular, we are interested in generating a library of new cyclic peptidomimetics. The reversibility of the reaction, the matched stereo goals, and the dynamic combinatorial aspects are all of interest in this study.

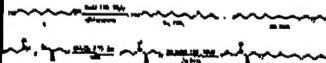


**MODEL STUDY**

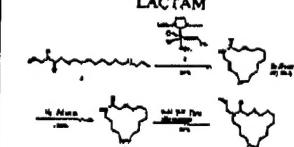
The preparation of a dynamic combinatorial library of peptides using the cross-metathesis of allyl esters of amino acids was examined in a model study. The preliminary investigation employed Grubbs' second generation catalyst for the ring-closing metathesis of unique macrocyclic systems. An N-methyl lactam function, that was part of the large oligo, was reacted with allyl esters of amino acids in a cross-metathesis coupling.



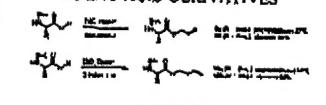
**SYNTHESIS OF DIENE**



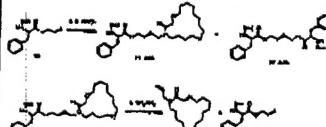
**LACTAM**



**AMINO ACID DERIVATIVES**

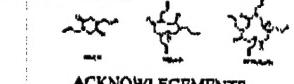


**CROSS-METATHESIS**



**CURRENT EFFORTS**

The Model Study has demonstrated the reversibility of the cross-metathesis reaction of an allyl ester of amino acid with N-methyl lactam, a key toward creating a dynamic library. Based on these studies, we are synthesizing N-methyl lactams with various numbers of "arms" (dimer, trimer, and tetramer). In the future studies, a small library of cyclic peptidomimetics will be generated. Various template are now being examined to shift the equilibrium where only one major equilibrium of the library is present. Results of these studies will be released in the near future.



**ACKNOWLEDGEMENTS**

• Student Group Members:  
Jed Hwang, Sophie Klein, Ryan Martin, and Kalyan Mendal

\*Reference:  
1. Low, T. C. et al. *J. Am. Chem. Soc.*, 122, 28-31  
2. Low, T. C.; Hwang, J. D.; Klein, S.; Martin, R.; Mendal, K. *J. Am. Chem. Soc.*, 123, 12242  
3. Low, T. C.; Hwang, J. D.; Klein, S.; Martin, R.; Mendal, K. *J. Am. Chem. Soc.*, 123, 12242

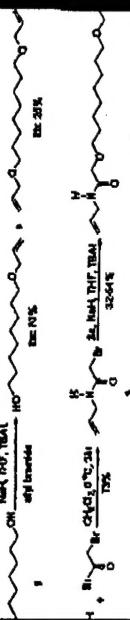
# Ring-Closing Metathesis of Macroyclic Compounds and Cross-Metathesis of Allyl Ester of Amino Acids Leading to Peptidomimetic

TAMMY K. C. LOW and ERIC J. ENHOLM

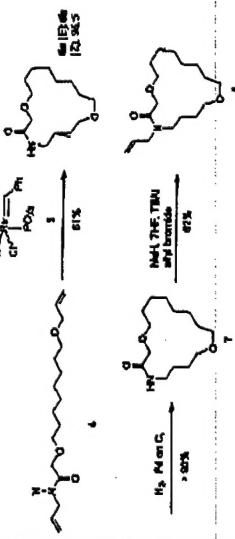
## INTRODUCTION

Ring-closing and cross-metathesis are important tools in organic synthesis<sup>1</sup>. The reversibility of cross-metathesis makes it ideal for use in dynamic combinatorial chemistry. In particular, we are interested in generating a library of new cyclic peptidomimetics. The reversibility of the reaction, the modified amino acids, and the dynamic biomimetic aspects are all of interest in this study.

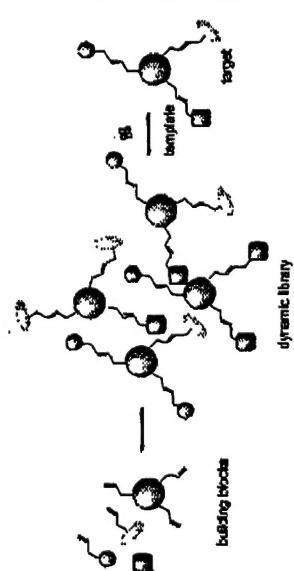
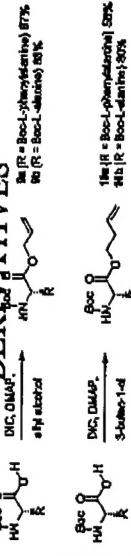
## SYNTHESIS OF DIENE



## LACTAM



## AMINO ACID DERIVATIVES



## MODEL STUDY

The preparation of a dynamic combinatorial library of peptides using the cross-metathesis of allyl esters of amino acids was examined in a model study. This preliminary investigation employed Grubbs' second generation catalyst for the ring-closing metathesis of unique macrocyclic systems. An N-allyl lactam function, that was part of the large ring, was reacted with allyl esters of amino acids in a cross-metathesis coupling.

## ACKNOWLEDGEMENTS

Enholm Group Members:  
Jed Hastings, Sophie Klein, Ryan Martin, and Kalyan Mandal

<sup>1</sup>Blackwell H. E. et al. *J. Am. Chem. Soc.* 2000, 122, 56-71  
<sup>2</sup>Frechman, J. F.; Eisinger, R. M. *J. Am. Chem. Soc.* 2000, 122, 2335-2344  
<sup>3</sup>Frechman, J. F. *J. Am. Chem. Soc.* 2004, 126, 1031-1042

